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Allergic reactions to COVID-19 -vaccinations – unveiling the secret(s)

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Abbreviations

ARIA, Allergy and Its Impact on Asthma

CAPR, complement activation-related pseudoallergy

COVID-19, Coronavirus Disease 2019

EAACI, European Academy of Allergy and Clinical Immunology

LNP, lipid nanoparticles

MHRA, British Medicines and Healthcare products Regulatory Agency

mRNA, messenger RNA

modRNA, nucleoside-modified messenger RNA

PEG, polyethylene glycol

SARS, Severe Acute Respiratory Syndrome

SARS-CoV-2, Severe acute respiratory syndrome coronavirus type 2

SmPC, summary of product characteristics

Since the beginning of the current pandemic our journal has published a series of important mechanistic and clinical reports of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection and
Coronavirus Disease 2019 (COVID-19) aimed to keep our readership up-to-date on all relevant developments in this world-wide crisis (1). This issue of *Allergy* features articles with current information on allergy-related questions regarding COVID-19 vaccination.

The article by Rodriguez-Coira and Sokolowska highlights recent developments and achievements in COVID-19 vaccination programs throughout the world and provides the readership with detailed information on "*classical*" technologies and novel vaccination mechanisms of action (2), including mRNA-based vaccines. One of the advantages of this approach is the feasibility of mass production and the possibility of rapid modification of antigens in case of spontaneous mutation of SARS-CoV-2. Moreover, the authors discuss open questions concerning the mRNA vaccine approach regarding the (long-term) efficacy of delivery and the possibility of a short half-life of viral mRNA within the cell which could reduce immune memory. This is the first vaccine for protection from COVID-19 that has been granted marketing authorization to be used in mass vaccination. It is an mRNA-based vaccine, BNT162b2 (European trade name "*Comirnaty*" (3)), a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2, which is embedded in lipid nanoparticles (LNP). Many other COVID-19 candidate vaccines are currently in preclinical and clinical development (4) of which some may obtain marketing authorization in due future.

Shortly after initiation of the BNT162b2 vaccination -campaign in the United Kingdom (UK), two cases of anaphylaxis were reported on the 9th of December 2020 by the British Medicines and Healthcare products Regulatory Agency (MHRA), (5) which prompted the unmet need for further clinical evaluation and research on the potential mechanisms involved.

In their report, Cabanillas et al. focus on the allergenic potential of the excipients in BNT162b2 and discuss the possibility that the LNP (ALC-0159)-compound, 2-[(polyethylene glycol (PEG))-2000]-N,N-ditetradecylacetamide, present in this vaccine may have caused the reported systemic reactions (6). The authors review former reports of PEG as a high-risk hidden allergen in drugs, cosmetics and food products and

conclude that the potential risk of PEG for sensitized patients should be further evaluated (6). In a Correspondence to this, Krantz et al. summarize PEG and potentially cross-reactive polysorbate 80 as excipients in different therapeutics and extensively discuss IgE-mediated mechanisms causing anaphylactic reactions to PEG (7). In addition, plausible mechanisms, such as complement activation, and molecular weight thresholds of PEG allergenicity are discussed. The authors recommend that patients with previous immediate reactions, such as PEG-induced anaphylaxis, vaccination with BNT162b2, further mRNA candidates and PEGylated products should be avoided until the individual risks are assessed by an allergist. Furthermore, the underlying mechanisms of these reactions triggered by mRNA vaccines should be better characterized. This important investigation is regarded as crucial for the development of mRNA vaccines in general, including those concerning other viruses and cancer (7). In their reply to this Correspondence, Cabanillas et al. add that although there is a broad range of delivery routes for PEG and PEG-analogues (e.g., the skin, gastrointestinal mucosa, conjunctiva, intramuscularly, intravenously and others) and the immune system is regularly exposed to these excipients, allergic sensitizations are rare and the underlying mechanisms have not been fully elucidated (8). In agreement with Krantz et al., the authors speculate on the important role of molecular weight for bioavailability in different body compartments and indicate further non-IgE-mediated hypersensitivity reactions, including complement activation-related pseudoallergy (CAPR) that involves anaphylatoxins (C3a and C5a) and anti-PEG IgM and IgG antibodies, which has been described for certain PEGylated drugs (9). Furthermore, they discuss other immunological pathways for hypersensitivity reactions to mRNA vaccines other than PEG-induced, such as mast cell activation and direct degranulation, especially in mastocytosis patients (8). In addition to the table provided by Krantz et al. listing PEG-containing drugs, the authors point out a group of PEG- and polysorbate-containing drugs, PEG-coated antihistamine tablets and PEG-containing corticosteroids that may be included as antiallergic medication in emergency kits for anaphylactic reactions, but should not be administered to patients with documented hypersensitivity reactions to PEG or its derivatives.

A first information and Position Paper of the "*Allergy and Its Impact on Asthma*" (ARIA-) initiative together with the European Academy of Allergy and Clinical

Immunology (EAACI) aims to provide preliminary recommendations on vaccination for COVID-19 based on current data from clinical (pivotal-)trials but also from international pharmacovigilance -reports after initiation of the mRNA vaccination program (10). The Position Paper states that patients with mild and moderate allergies should not be excluded from vaccination programs as this may put population (herd-)immunity at risk due to the high prevalence of allergic diseases. There is a current need to improve our understanding of the nature of the reported allergic reactions, the medical background of patients and causal underlying immune mechanisms. Moreover, it is advised that healthcare providers involved in vaccination programs should be trained to recognize signs of anaphylactic reactions in vaccinated patients and be prepared to treat accordingly, including the administration of adrenaline. Vaccinated individuals should be observed for at least 15 minutes after vaccination. In their statement, the authors conclude that based on the current evidence the "*benefit of the vaccination clearly outweighs the risk of severe COVID-19 development including the more than 30% of the population suffering from allergic diseases*" (10).

This is in line with the marketing authorization recently granted in the European Union which does not contain contraindications for individuals with allergies or persons with medical history of anaphylactic reactions (3). However, a previously known allergy to the substances contained in the vaccine (e. g. PEG) presents a contraindication, as well as a reaction to the first dose of the COVID-19 vaccine, which presents a contraindication for administering the second dose. In compliance with the European SmPC (3), a post-vaccination follow-up observation of at least 15 minutes should take place for all vaccinated individuals. In the event of a serious allergic intolerability reaction after administration of the vaccine, appropriate medical treatment and supervision should always be available.

During the post-marketing authorization period, the regulatory agencies and the national competent authorities recommend further monitoring of hypersensitivity events. To identify the factors and risk groups for serious hypersensitivity reactions, it is of utmost importance to obtain detailed case-related information (11) through the European register for spontaneous reports and to apply the same criteria to describe anaphylactic reactions to vaccines. The World Health Organization and regulatory

authorities recommend following the Brighton Collaboration-criteria for anaphylaxis (12).

Taken together, this special issue on "COVID-19 vaccination" provides the readership with the most recent literature and helpful clinical guidance on pressing questions regarding vaccination as one of the main drivers in controlling the current pandemic in 2021. Based on these first reports, further scientific discoveries are expected to be 'unveiled' in the near future.

Conflict of Interests: Dr. Pfaar reports grants and personal fees from ALK-Abelló, Allergopharma, Stallergenes Greer, HAL Allergy Holding B.V./HAL Allergie GmbH, Bencard Allergie GmbH/Allergy Therapeutics, Lofarma, grants from Biomay, grants from Circassia, grants and personal fees from ASIT Biotech Tools S.A., Laboratorios LETI/LETI Pharma, personal fees from MEDA Pharma/MYLAN, grants and personal fees from Anergis S.A., personal fees from Mobile Chamber Experts (a GA2LEN Partner), personal fees from Indoor Biotechnologies, grants and personal fees from Glaxo Smith Kline, personal fees from Astellas Pharma Global, EUFOREA, ROXALL Medizin, Novartis, Sanofi-Aventis and Sanofi-Genzyme, Med Update Europe GmbH, streamedup! GmbH, grants from Pohl-Boskamp, Inmunotek S.L., personal fees from John Wiley and Sons AS, Paul-Martini-Stiftung (PMS). Vera Mahler indicates, that the views expressed in this editorial are the personal views of the author as an expert in the field of allergology and may not be understood or quoted as being made on behalf of or reflecting the position of the respective national competent authority, the European Medicines Agency, or one of its committees or working parties. She has no conflict of interest to disclose.

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